

There are many good courses on EBM, but there is no better way to understand the intellectual poverty of much research than to actually do a systematic review. Employers should encourage employees to get stuck in. The benefits resulting from better-informed and more experienced people will show in no time.

Short-term secondments from the NHS to academia, or to and from industry, can help cross-fertilisation of ideas. *Bandolier* is pleased to be able to help in this edition by carrying job advertisements (at no charge) for the Centre for Reviews and Dissemination, and for Pfizer, which is setting up an in-house evidence-based medicine department. Much of the health care industry has been trying to understand what evidence-based medicine means to them, and *Bandolier* hopes that other companies will follow Pfizer's lead.

Electrons whizz

Many vacancies for doctors in the UK are now advertised electronically on doctors.net at <http://www.doctors.net.uk/>. Doctors.net puts up job adverts completely free of charge to the NHS. For details contact Heidi Laughton: heidi@mess.doctors.org.uk; Phone: 01235 828401; Fax: 01235 862791.

Doctors.net also has the Cochrane Library completely free of charge to all its members. In the South and West Region you can also get the Cochrane Library free at <http://www.update-software.com/clibhome/swreg.htm>.

Bandolier conference on pain

"Pain - where's the evidence" is the title of *Bandolier* conferences planned for London and Manchester on July 6 and 8. Fax 01865 226978 for details.

In this issue

Endogenous hormones and fractures	p. 1
Exercise and bone density	p. 3
HRT and hip fractures	p. 3
Tibolone and bone density	p. 4
Alendronate and fractures	p. 4
Antibiotics for childhood coughs	p. 6
Decision-making in healthcare	p. 7
Hyperbaric oxygen for MS	p. 8
Evidence-based job adverts	p. 8

The views expressed in Bandolier are those of the authors, and are not necessarily those of the NHSE

MATTERS POSTMENOPAUSAL

Bandolier has written before (25, 37) about hip fractures, and how devastating these are for people who suffer them. Elderly persons with a hip fracture are unlikely to regain their independence, and some degree of permanent disability is probable. Hips and other bones will fracture for different reasons, but osteoporosis will be a major factor in the elderly, especially women.

Endogenous hormones

Oestrogen has important effects on bone metabolism. Lack of it increases the risk of bone resorption together with loss of mineral results in bones getting progressively weaker. The importance of oestrogen is shown by a study on how endogenous oestrogen affects the risk of hip and vertebral fractures in older women [1].

Study

Between 1986 and 1988 just under 10,000 women aged 65 years or more were recruited in four US cities. They were asked about lifestyles, oestrogen replacement, and multi-vitamin and calcium use. X-rays of the spine and bone mineral density measurements were taken, together with blood samples for measurement of a variety of hormones. The women were then contacted by mail every four months to identify fractures. Follow up was more than 99% complete. Follow up spine X-rays were obtained in the 79% of the women still alive at 3.7 years.

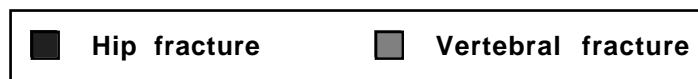
A random selection was made of 133 of the 332 women who had a hip fracture and 138 of the 359 women with a new vertebral fracture, together with control groups randomly selected and twice to three times the number.

Results

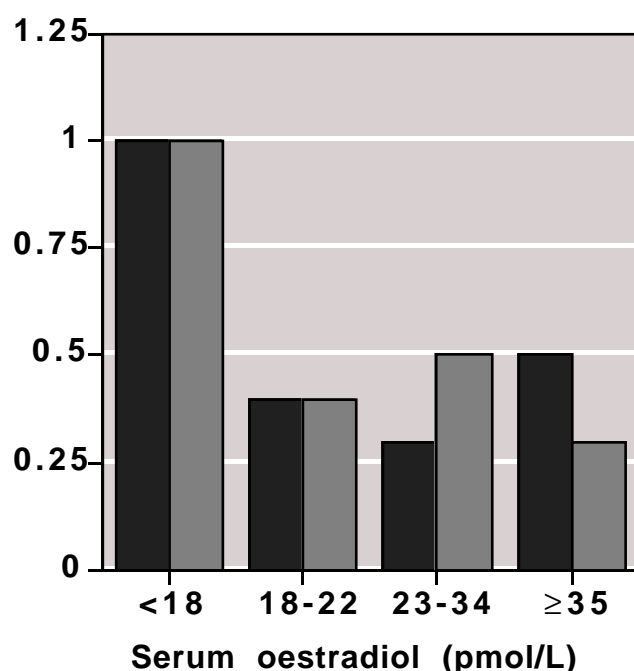
Women were well matched at baseline for calcium and vitamin D supplementation and intake, though women with fractures were older, lighter and had lower bone density. After adjustment for weight and age two hormones were particularly associated with increased risk of fracture of the hip or vertebrae.

A serum oestradiol that was undetectable (<18 pmol/L) was associated with a relative risk of about 2.5 (1.4 to 4.4). Any increase in serum oestradiol above the limits of detection slightly more than halved the risk of a fracture (Figure, overpage).

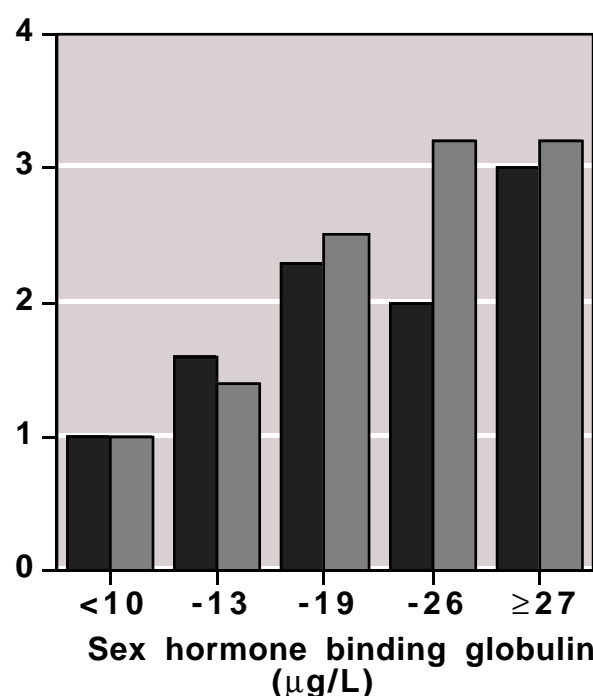
Effect of endogenous oestradiol and sex hormone binding globulin on risk of fracture



Relative risk of fracture



Relative risk of fracture



A serum sex hormone binding globulin of ≥ 10 $\mu\text{g/L}$ was associated with a relative risk of 2.1 (1.1 to 4.2). Any increase in sex hormone binding globulin above 10 $\mu\text{g/L}$ resulted in progressive increases in the risk of fracture, up to three-fold at the highest concentrations found (Figure).

Women with undetectable levels of oestradiol and measurable sex hormone binding globulin had a much increased risk of fracture, even when adjustments were made for age and weight (Table).

Comment

Sex hormone binding globulin binds oestradiol into a form that is not immediately available to tissues. Both increases in sex hormone binding globulin and low levels of oestradiol work in the same way - to starve tissues, including bone, of available oestrogen. This important study dramatically highlights the importance of oestrogen as a risk factor for hip and vertebral fractures. If the associations were causal,

they would account for a substantial proportion of fractures in elderly women. There may even be a suggestion that women particularly at risk could be identified by blood tests, and remedial therapy instituted. *Bandolier* does not leap to the conclusion that screening is the answer, or an answer, but there is an opportunity here to further explore this interesting area. It could be one of those topics where diagnostic tests and treatment together make good sense.

These results also give some biological plausibility for the effects of Soya (*Bandolier* 56). Soya isoflavonoids are weakly oestrogenic, and probably provide a low level of oestrogenic "cover". Whether they have effects on hip and vertebral fractures still has to be clarified.

References:

- 1 SR Cummings et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. *New England Journal of Medicine* 1997 339: 733-738.

Relative risk (95% CI) for fracture in women with undetectable levels of oestradiol and measurable sex hormone binding globulin

	Hip fracture	Vertebral fracture
Age adjusted	14 (3.0 to 62)	12 (3.3 to 41)
Weight adjusted	6.9 (1.5 to 32)	7.9 (2.2 to 28)

EXERCISE AND BONE DENSITY

Exercise is good for us, whatever the reason we do it. Younger women are advised to take aerobic exercise as a way of attaining and maintaining peak bone mass in order to ameliorate postmenopausal bone losses and to provide some protection against fractures later in life. Does aerobic exercise have effects on bone density in postmenopausal women? A systematic review [1] says that the evidence is sparse and effects lacking.

Search

The search was limited to MEDLINE from January 1978 looking for English language papers only; 1978 was chosen since this was the year when bone mineral density measurements became useful. Trials had to have a comparison nonexercise group and look at bone density at the hip.

Results

Six studies were found, only two of which were randomised. Women included had ages from the early 60s to mid 70s and who exercised for up to one year. The randomised studies had most of the women studied - 134 in total, though because of subgroups, with and without calcium supplementation, numbers in any particular group were small.

While there was an intensively statistical approach, the raw results were simple. Whether measurements were made at the femoral neck, trochanter or Ward's triangle, with or without calcium supplementation, there were no measurable changes in bone density after exercise compared with before exercise or with nonexercise controls.

Comment

Disappointing that there is not more information. Certainly insufficient information on which to base any recommendations, apart from the fact that exercise is a good thing for many other reasons.

- 1 GA Kelley. Aerobic exercise and bone density at the hip in postmenopausal women: a meta-analysis. Preventive Medicine 1998 27: 798-807.

HRT AND HIP FRACTURES

Replacement of endogenous with exogenous oestrogen reduces the risk of hip fracture, as a large case-control study from Sweden shows [1].

Study

All hip fractures between late 1993 and early 1995 in women born in 1914 or after in six Swedish counties covering about 4.3 million people were found from hospital discharge records. After excluding those for which there was an obvious cause (trauma, dementia, cancer etc) there were 1644 cases. Controls (over 3000) were women born in Sweden randomly selected from a population register.

Cases were sent a comprehensive questionnaire about three months after the fracture. Controls were sent the same questionnaire. This asked about reproductive history and use of exogenous oestrogens, including oral contraceptives and hormone replacement therapy, as well as demographic, dietary and other questions.

Results

Eighty-two percent of women answered the questionnaires. The main results are shown in the Table. Compared with never users, there was a substantial decrease in fracture risk with ever users of replacement therapy, though this came predominately from the reduced risk for current users. For current users there was a 9% decrease in risk of hip fracture for every year of use. Five years after the last use of hormone replacement therapy no substantial protective effect against hip fracture remained, though a protective effect was seen in the five years after use of hormones when they had been used for at least five years (Table).

In sub-group analyses a common finding was that these general results were much the same irrespective of the type of hormone replacement therapy. Oral or transdermal therapy, with or without progestins, all had much the same protective effect for current users, and protective effects were evident with progestins structurally related to progesterone and to testosterone.

Main results on hip fracture risk and HRT use

	Odds ratio* (95% CI)	Percent risk decrease for each year of therapy (95% CI)
Ever user	0.58 (0.46 to 0.75)	6 (3 to 9)
Current users of HRT	0.35 (0.24 to 0.53)	9 (5 to 13)
Former users	0.76 (0.57 to 1.01)	3 (7 to -2)
Last use 1-5 years, duration >5 years	0.27 (0.08 to 0.94)	not applicable

* compared with never users of hormone replacement therapy

Comment

The key message is that hormone replacement therapy protects against hip fracture while it is being taken and for a few years afterwards. Continued protection needs continued use.

Reference:

- 1 K Michaëlsson et al. Hormone replacement therapy and risk of hip fracture: population based case-control study. *British Medical Journal* 1998 316: 1858-1863.

TIBOLONE AND BONE DENSITY

Postmenopausal women may use hormone replacement therapy to combat climacteric symptoms of flushing, mood changes and loss of libido. Particularly if they are younger, regimens containing oestrogens which result in regular vaginal bleeding may be appropriate. Older women starting hormone replacement therapy and who may not have been exposed to oestrogens for many years probably find vaginal bleeding and breast fullness accompanying oestrogen inappropriate. "I can't be doing with that!" was one response *Bandolier* has come across.

Data on the newer versions of hormone replacement therapy have yet to appear on *Bandolier's* desk, but there is a systematic review of tibolone, a steroid with mixed effects on tissues [1] and with which vaginal bleeding is rare. Long-term studies on the effects of tibolone on fracture rates have not been done, but effects on the surrogate measure of bone mineral density show increases of the same magnitude as with alendronate.

Review

The review sought all clinical studies which examined effects of tibolone on climacteric symptoms, bone, breast, endometrium, metabolism and the vagina, as well as in add-back therapy in endometriosis using a variety of strategies.

Results

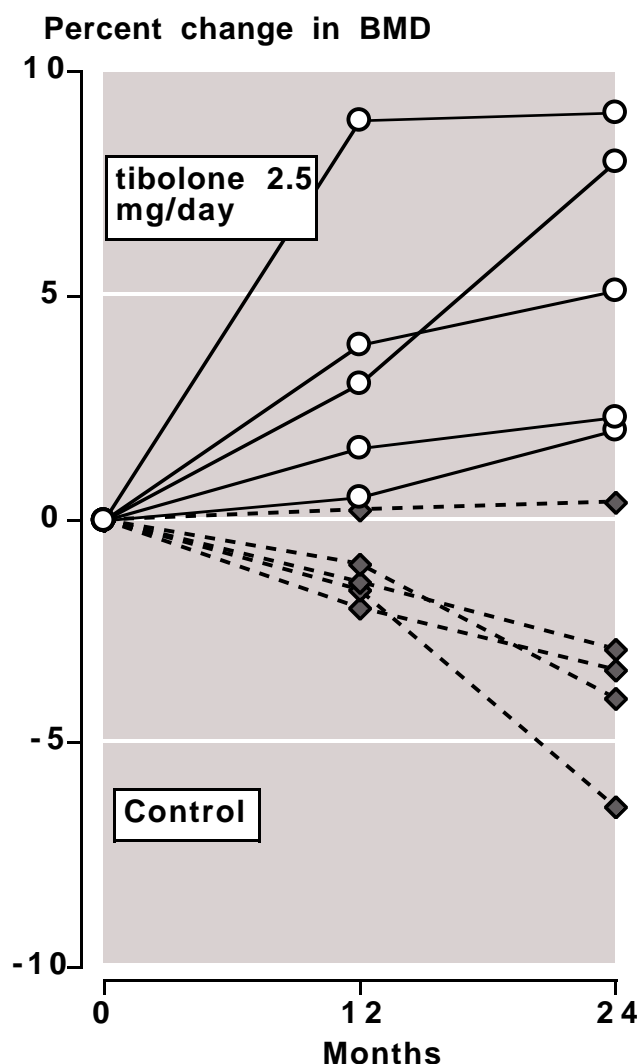
Four randomised and one non-randomised study examined bone mineral density in the lumbar spine, and the Figure shows percentage changes for the usual dose of 2.5 mg a day and in placebo or no treatment controls over two years. These and other studies also showed increases in bone mineral density at other sites, like phalanges, and the hip.

Tibolone was also effective in combating flushes, in increasing libido, and in reducing symptoms of vaginal dryness.

Comment

The main indications for tibolone seem to be for women more than one year after their last menstruation. A hormone replacement therapy with little oestrogenic effect on the breast and endometrium, but with powerful effects on bone, might also be an option in older women to reduce bone loss and help prevent fractures.

Change in bone mineral density in the lumbar spine in four randomised and one nonrandomised trial



Reference:

- 1 RA Moore. Livial: a review of clinical studies. *British Journal of Obstetrics and Gynaecology* 1999 106 Suppl 19: 1-21.

ALENDRONATE AND FRACTURES

One of the options for trying to prevent fractures in postmenopausal women is the use of bisphosphonates. A new, large, randomised trial shows who is likely to benefit with alendronate, and the extent of that benefit [1].

Study

From over one million women contacted by mail, 2214 were eventually randomised to alendronate and 2218 to placebo in 11 centres. The blinded treatments were alendronate 5 mg per day for the first two years, increased to 10 mg per day at the second annual visit because other trials suggested this dose had greater effects on bone mineral density. Women had to be 50 to 85 years old, postmenopausal for at least two years and have a femoral neck bone mineral density about two standard deviations below the mean of nor-

NNTs with alendronate in postmenopausal women

Type of fracture	Alendronate number/total	Placebo number/total	NNT (95% CI)
All patients			
Clinical fractures except spine, hip and wrist	182/2214	227/2218	50 (27 to 321)
Vertebral fractures	43/2214	78/2218	64 (39 to 162)
Patients with lowest bone mineral density			
Clinical fractures (all)	107/819	159/812	15 (10 to 34)
Vertebral fractures	22/819	44/812	37 (22 to 122)

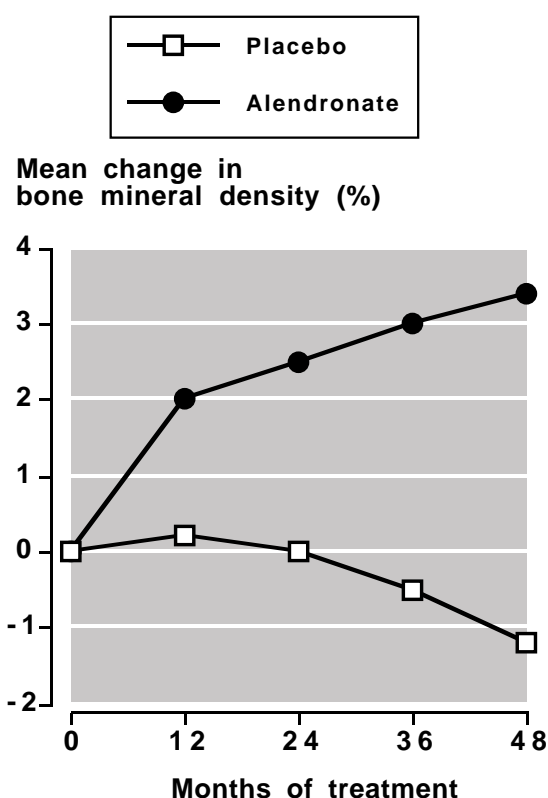
mal young adult white women. There were exclusions for various medical problems and consumption of exogenous oestrogens.

There were frequent visits over four years for bone mineral density measurements and a spine X-ray at the end of the study. The primary outcomes were clinical fractures (non-spine fractures of hip, arm, wrist etc) and radiological vertebral fractures.

Results

The groups were comparable at baseline. There was a significant effect of alendronate on bone mineral density - data for the femoral neck over four years is shown in the Figure.

**Femoral neck bone mineral density
over 48 months with**



There was no significant effect of alendronate on the risk of all clinical fractures, though the number of fractures at sites other than the hip, wrist or spine (70% of the total clinical fractures) was reduced by alendronate (relative risk 0.79, 95% CI 0.65 to 0.96). The number needed to treat (Table) with alendronate over four years to prevent a fracture other than at the hip spine or wrist was 50 (27 to 321).

Alendronate also reduced the number of women with at least one radiological vertebral fracture (relative risk 0.56, 95%CI 0.39 to 0.80). The number needed to treat with alendronate over four years to prevent at least one radiological fracture of the spine was 64 (39 to 162).

A planned subgroup analysis examined the effect of alendronate according to the bone mineral density at the femoral neck. Significant effects of alendronate were found in women whose bone mineral density was more than 2.5 standard deviations below that of young white women, a definition which covered about 37% of women in the study.

Clinical fractures (all sites) were significantly reduced in this group by alendronate, with a relative risk of 0.64 (0.50 to 0.82) and a number needed to treat over four years of 15 (10 to 34) to prevent any clinical fracture. For radiological vertebral fractures the relative risk was 0.50 (0.31 to 0.82) and the number needed to treat was 37 (22 to 122).

Comment

This was a large trial directed towards women most at risk of fracture because of their low bone mineral density. Perhaps its most significant feature was that it further identified those women with the lowest femoral neck bone density who would benefit most from alendronate treatment, and who could be identified using an increasingly available diagnostic test. This combination of test and treatment efficacy should simplify guidance and maximise quality and value for money.

Reference:

- 1 SR Cummings et al. Effect of alendronate on risk fracture in women with low bone density but without vertebral fractures. JAMA 1998 280: 2077-2082.

ANTIBIOTICS FOR CHILDHOOD COUGHS

Another winter with its colds and coughs and grumpy people complaining either that their GP wouldn't give them or their children antibiotics, or if they did, the antibiotics didn't help. It sent *Bandolier* scurrying to find the systematic review [1] which showed the evidence that doctors don't prescribe antibiotics for colds for very good reasons.

Review

The review used an extremely broad search to find placebo-controlled studies of antibiotics in infants and children aged 0-12 years with onset of upper respiratory tract infection in the preceding two weeks. Infection was a pragmatic definition of acute inflammation of the nasal or pharyngeal mucosa in the absence of other defined respiratory infection.

Outcomes

These were:

- 1 How many children were worse or unchanged on days 5-7.
- 2 How many children suffered complications or progression of illness (otitis media, pharyngitis, bronchitis or pneumonia).
- 3 How many children had adverse effects (diarrhoea, vomiting, rash etc).

Results

Ten studies that matched the inclusion criteria were found, published between 1956 and 1994 and conducted in a variety of settings around the world. Four had no extractable data, and three of these concluded that antibiotics were of no benefit.

Results for the remaining six (1,700 children) were pretty uncompromising. For the proportion of children in whom the clinical outcome was unchanged or worse at 5-7 days there was no significant difference between antibiotic and placebo (Figure), with a relative risk of 1.0 (0.9 to 1.1).

There was no difference between antibiotic and placebo in the number of children with complications or progression of illness (Figure), with a relative risk of 0.7 (0.5 to 1.1). There was no difference between antibiotic and placebo in the number of children with adverse effects, with a relative risk of 0.8 (0.5 to 1.2).

Comment

The wide variation in event rates seen in the Figure is not unusual, and probably reflects the wide temporal and geographic spread of the trials. There

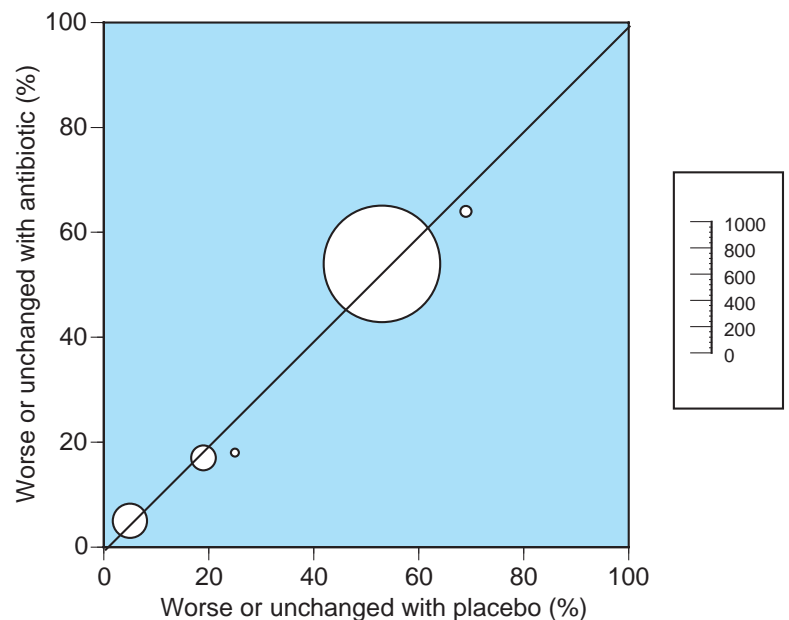
was no evidence that giving children antibiotics for uncomplicated upper respiratory tract infection has any value. Given the widespread concerns about antibiotic resistance, it probably does more harm than good.

Reference

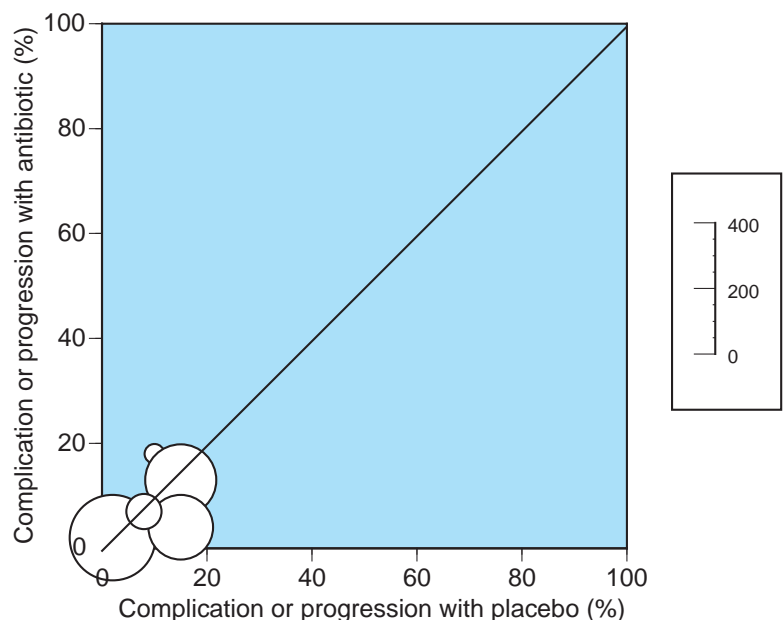
- 1 T Fahey, N Stocks, T Thomas. Systematic review of the treatment of upper respiratory tract infection. *Archives of Diseases in Childhood* 1998 79: 225-230.

Effect of antibiotics in children with upper respiratory tract infections

1: clinical outcome at day 5-7



2: complications or illness progressed



DECISIONS, DECISIONS!

Occasionally it is instructive to see how evidence is used in making decisions in areas outside medicine. There are two external and two internal examples that *Bandolier* has found recently which made us think just how similar processes can be.

Validity and causation

Suppose you had data which showed that there was a highly significant inverse correlation between central bank independence and inflation: low inflation occurred in countries with highly independent central banks. The obvious decision, if you wanted low inflation, would be to create an independent central bank, and that has been a major tenet of economic thinking for a decade or so.

James Forder's trashing of this theory [1] originates in the fact that measures of central bank independence were so poor and inconsistent as to deny any relationship. We can't measure independence, so can't pontificate as to causation.

Health care decisions likewise require outcomes which make sense, and in whose measurements we can trust. Too often we see research papers or reviews whose only safe home is in the bin. *Caveat lector*: we have to be vigilant.

Feel the width

However much information we have, actually making a decision is often hard. Derek Pooley, faced with decision-making on renewable energy sources, used the simple guide of cost per tonne as a way of sharpening the mind [2]. This is a bit like a cost per QALY (the quality-adjusted life year) used in health care. Many people think it a crude measure, but since fine measures are unavailable (and may be impossible to get anyway), it has to serve. Ceri Phillips gives a good explanation of QALYs and costs [3], and some illustrative costs per QALY are shown in the Table.

Cost per QALY for healthcare interventions

Intervention	£/QALY (1990 prices)
Neurosurgical intervention for head injury	240
GP advice to stop smoking	270
Neurosurgical intervention for subarachnoid haemorrhage	490
Antihypertensive treatment to prevent stroke (45-69 years)	940
Pacemaker implant	1,100
Hip replacement	1,180
CABG (left main vessel disease, severe angina)	2,090
Kidney transplant	4,710
Heart transplant	7,840
Home dialysis	17,260
Hospital dialysis	21,970

Quick and clean

Just how to use cost per QALY in health care decision-making is shown in a superb paper from Andrew Stevens and his colleagues from Wessex in 1995. This paper, which draws together all the themes in making decisions about new interventions, should be required reading. It provides guidance for ordering one's thoughts.

Decision-making on evidence and cost

Cost per QALY (£,000)

Evidence	<3	3-20	>20	Negative
I	Strongly support	Strongly support	Limited support	Not supported
II	Strongly support	Supported	Limited support	Not supported
III	Supported	Limited support	Limited support	Not supported
IV	Not proven	Not proven	Not proven	Not proven

The paper also introduces Buxton's Law: "it is always too early to evaluate a new technology until unfortunately suddenly it's too late". It sets out seven stages needed for assessing technology (loaded towards the new, but highly applicable to existing technologies), and emphasises the importance both of analysis – drawing together information from a wide range of sources to bolster evidence from systematic review and meta-analysis – and costs – which have to be dealt with pragmatically.

They give us a simple-person's guide to making decisions based on levels of evidence and cost per QALY. Pragmatism is the name of the game. If, for instance, costs are lower than £3,000 per QALY, then the need for randomised trials may be relaxed. It is worth having a copy of this thoughtful and influential paper on your desk for re-reading at quiet moments.

References:

- 1 J Forder. The case for an independent European central bank: a reassessment of evidence and sources. *European Journal of Political Economy* 1998 14: 53-71.
- 2 D Pooley. Prospects for renewable energy sources in the United Kingdom. *Proceedings of the Royal Society of Edinburgh* 1987 92B: 73-89.
- 3 C Phillips & G Thompson. What is a QALY? RPR Educational Series published by Hayward Medical plc: available on www.hayward.co.uk, or in hard copy by calling 01638 751515
- 4 A Stevens, D Colin-Jones, J Gabbay. Quick and Clean: authoritative health technology assessment for local health care contracting. *Health Trends* 1995; 27: 37-42.

Bandolier's piece on interferons for MS (*Bandolier* 58) drew requests for evidence on the effectiveness of hyperbaric oxygen. We thought this was known to be ineffective, but it appears still to be a topic of interest. We found a helpful systematic review [1] carried out a few years ago.

Review

The review used a comprehensive searching strategy to find controlled studies in which hyperbaric oxygen at about two atmospheres was compared with a control group (usually normal air or gas mixture without oxygen enrichment at lower pressures, usually at or just above one atmosphere) in patients with multiple sclerosis. The approach was to grade all the 14 trials found against 10 criteria for methodological assessment. These included items like randomisation and blinding, size, inclusion criteria etc.

Trials which scored 7 out of 10 or more on these criteria went on for further analysis. One of the eight trials included was not randomised, and four of the six excluded were randomised. All of the included studies were double blind.

Results

The reviewers used changes in EDSS (*Bandolier* 58), a scale that sets out to measure functional ability in multiple sclerosis. The mean score at entry in most trials was 5 to 6.5, which indicates a moderate disability. The mean age of patients was early to mid 40s with an average duration of disease of 12-14 years. Apart from the original trial of hyperbaric oxygen in 1983, none of the others provided any evidence for a beneficial effect of hyperbaric oxygen. The reviewers also mentioned that there was no evidence for improvement in other areas like bladder function. Adverse effects were minor.

Comment

Profoundly negative, if somewhat unsatisfying. Actual data extracted from the individual trials are not presented, and while that may be understandable, it does mean one is totally dependent upon the judgement of the reviewers. A re-analysis might, for instance, concentrate on the randomised trials given the well understood bias found in non-randomised trials.

Purchasers who buy hyperbaric oxygen therapy for multiple sclerosis might need an updated review before changing practice because they will need to persuade patients and their carers that it does no good. It probably isn't cheap either, and with limited funds it would be appropriate to ask whether better value for money couldn't be obtained from interventions with known efficacy. *Bandolier* could find no new randomised trials published since the review was completed.

1 J Kleijnen, P Knipschild. Hyperbaric oxygen for multiple sclerosis: Review of controlled trials. *Acta Neurologica Scandinavica* 1995 91: 330-334.

Centre for Reviews and Dissemination

The NHS Centre for Reviews and Dissemination (CRD) is looking for two 12-month senior secondments to carry out research, starting in Summer 1999. "We are able to offer an attractive salary and other benefits associated with working in a major University research department." One post would involve work in CRD's existing systematic review programme and the second would require a person to lead on the updating of CRD's internationally recognised guidelines for undertaking systematic reviews. Both posts would offer the opportunity for researchers to further develop their skills in review methodology as well as gaining experience from the work of a major contributor to the NHS R&D Programme.

Experienced researchers who already have some expertise in systematic reviews and who would be happy to take a 12 month break from their host institution should contact Professor Jos Kleijnen (Tel 01904 433647 or Email jk13@york.ac.uk).

Head of Evidence Based Medicine, Pfizer

This is a new position, reporting to the Medical Director and responsible for:

- Establishing an Evidence Based Medicine (EBM) Group within the UK Medical Department, which will be the source of information and expertise on EBM within the company.
- Proposing EBM strategies and programmes, working closely with the Therapeutic and Product Teams.
- Conducting systematic reviews in line with product plans.
- Providing high-quality responses to requests for EBM and systematic reviews from external customers.

Initially based at Sandwich it will relocate to Reigate in 2000. Send a CV and covering letter, or telephone to discuss further before applying to Dr John Padbury, Talentmark Search and Selection, King House, 5-11 Westbourne Grove, London W2 4UA. Tel: 0171 229 2266. Fax: 0171 229 3549. E-mail: John.Padbury@Talentmark.com

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